REMARKS

The Official Action of February 26, 2003 has been carefully considered and reconsideration of the application as amended is respectfully requested.

Independent claims 11 and 16 have been amended more clearly to distinguish over the prior art, as discussed below. The amendments to these claims draw clear support from the specification as filed at, for example, page 9, first paragraph and the examples on page 14-15 which show that the gametocytocidal activity of the claimed compound of formula (1) inhibits the transmission of malaria by reducing gametocyte infectivity to mosquitoes (see also discussion below). The recitations pertaining to the administered amounts of the compounds, as recited in claims 11 and 16, draw clear support from the specification as filed at, for example, the paragraph bridging pages 15-16 (daily dose) and page 14, first paragraph (single dose). Claim 19 has been replaced with new claim 23, which has been made dependent from claim 11.

PRIOR ART REJECTIONS

The claims stand rejected under 35 USC 102(b) as allegedly being anticipated by Paliwal or Saxena. Applicants respectfully traverse these rejections.

Claimed Invention

The claimed invention is based on Applicants' discovery that the recited compound of formula (1) has gametocytocidal activity that can be used to inhibit the

transmission of malaria. To explain, there are basically three identifiable biological pathways (Carson 1955, WHO 1955), which individually or collectively may be employed for the treatment of malaria. These three pathways may be categorized as:

(i) **Tissue schizontocidal:** Pathway preventing the development of the asexual stage of parasite (including hypnozoites) residing in the hepatocytes or the liver cells;

(ii) **Blood schizontocidal:** Pathway which prevents the development of the asexual parasite residing in the erythrocytes or blood cells; and

(iii) **Gametocytocidal:** Pathway which prevents the development of sexual parasite stages in the patients' blood, which on mosquito bite lead to development of oocyst in mosquito. The inhibition of this development stage would interrupt the transmission of malaria.

Interruption of any of the three distinct pathways amounts to treatment of malaria. There are defined and reproducible procedures and protocols to demonstrate the particular stage specific action of a new agent. Based on the practice of these procedures and protocols, it is emphasized that a given compound seldom possesses activity against all three distinct stages. It is therefore essential that the antimalarial effect against the different stages in the life cycle of the parasite be demonstrated separately even for the same agent. In the instant case the effectiveness of the compound of formula (1) in preventing the development of gametocytes is disclosed for the first time.

A significant aspect of malaria is its transmission from host to mosquito, which acts as the disease vector. Stopping transmission from infected host to mosquito is a significant step. Thus gametocytocidal activity (killing of sexual parasites) is of very high utility in malaria control programs throughout the world. Successful use of an effective gametocytocidal drug can interrupt malaria transmission and prevent infection to new cases. Even if the mosquitoes bite the persons treated with this agent it will not get infected and hence will not develop any infective stages for transmitting malaria infection to the healthy population. Mosquitoes engorging blood from a treated case will not carry the malaria infective sporozoits, which will ultimately stop fresh malaria cases in endemic areas.

The human portion of the malaria parasite life cycle involves invasion of sporozoites into heptocytes (liver) followed by its (parasite) differentiation within the hepatic cells into a multinucleated stage called schizont. Mature (hepatic) schizonts release merozoites that invade erythrocytes (red blood cell) and develop into asexual erythrocytic (blood stage) schizonts. The mature erythrocytic schizonts release merozoites, which invade other erythrocytes to continue the asexual erythrocytic cycle which is responsible for clinical manifestation of malaria.

Some merozoites infecting fresh RBC, instead, differentiate into male and female gametocytes (sexual stages) and await to be transferred through mosquito bite. The drug that kills these gametocytes in the hosts blood are called gametocytocidal agent. When transferred into mosquito gut these sexual stages develop into gametes,

which after fertilization fuse to develop into zygotes. These zygotes transform into ookinete, which penetrate the mosquito gut wall and grow into oocysts. The oocysts mature to release sporozoites which reach into salivary gland of the mosquito and are ready to infect new host during the mosquito bite.

As shown by the examples in the present specification, the claimed compound of formula (1) kills gametocytes within the erythrocytes in hosts' blood and the killed gametocytes are not viable to develop inside mosquito gut into oocyst as revealed in Table 1 of the specification. The specification at page 14 amply details that the oocyst development is completely blocked after treatment with the claimed compound of formula (1), and the same batch of mosquitoes also did not produce (show) any sporozoites. Hence the absence of sporozoites in the mosquitoes is additional demonstrative evidence in support of the inhibition of development of oocysts: thereby verifying the effectiveness of the claimed method for inhibiting transmission of malaria.

Distinctions over Prior Art

The Examiner considers the cited references to anticipate all of the claims through inherency, but Applicants respectfully note that all of the claims presently on file are limited to the administration of the recited amounts of the compound of formula (1). The Examiner has not referred to any portion of the cited references to show the claimed amounts. In fact, only the Saxena reference could even arguably be considered to suggest an amount to be administered, and this amount (8.75 mg/kg x 4

days) is outside of the claimed amounts. Moreover, there is nothing in the references to show or suggest with even a reasonable expectation of success that the administration to an animal of the claimed amounts of the recited formula (1) would be successful in reducing gametocyte infectivity to mosquitoes.

For the above reasons, it is respectfully submitted that the cited references do not set forth even a *prima facie* case of alleged anticipation or obviousness of the invention as now claimed. In any event, as discussed above, the gametocytocidal activity of the recited compound of formula (1) could not have been expected from its tissue schizontocidal or blood schizontocidal activities. Accordingly, even assuming for the sake of argument that the cited references did set forth a *prima facie* case of alleged obviousness, it is respectfully submitted that the evidence in the specification of the gametocytocidal activity of the claimed compound when adminsitered in the recited amounts would be sufficient to overcome such alleged *prima facie* case.

OTHER REJECTIONS/OBJECTIONS

With respect to the rejection under 35 USC 112, first paragraph, appearing at paragraph 5 of the Official Action and the objection appearing at paragraph 6 of the Official Action, it is respectfully submitted that the same have been overcome by the amendments to the claims discussed above.

In view of the above, it is respectfully submitted that all rejections and objections of record have been overcome and that the application is now in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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